right to communicate to consumers that their products have fewer side effects than drugs.

FDA does not believe that this provision precludes general statements about the function or mechanism of action of a dietary supplement. It is not necessary to claim that the product is a substitute for a drug or therapy to describe its function or its mechanism of action. Nor is § 101.93(g)(2)(vi) duplicative of § 101.93(g)(2)(v). Claiming that a product is a substitute for a specific drug or therapy, e.g., "Herbal Prozac," is a different means of communicating that a dietary supplement is intended to treat a disease than claiming that the product belongs to a class of drugs associated with treatment or prevention of that disease, e.g., "antidepressant."

FDA does not agree that section 403(r)(6) of the act permits a dietary supplement manufacturer to claim that its product has fewer side effects than a drug, if the drug is intended to treat or prevent disease, because the clear implication is that the dietary supplement is intended for treatment or prevention of the same disease. If, however, the drug is not intended to treat or prevent disease, a dietary supplement manufacturer is free to make truthful, non-misleading comparisons between the drug and the dietary supplement.

P. Augmentation of Therapy or Drug for Disease (§ 101.93(g)(2)(vii))

Under proposed § 101.93(g)(2)(vii), a statement would have been considered a disease claim if it explicitly or implicitly claimed that the product augmented a particular therapy or drug action. The preamble offered the following example of a disease claim under this criterion: "Use as part of your diet when taking insulin to help maintain a healthy blood sugar level." A claim that did not identify a specific drug, drug action, or therapy would not constitute a disease claim under this criterion. The preamble gave the following example of an acceptable structure/function claim: "use as a part of your weight loss plan."

(75.) Several comments supported this provision. A few comments requested that FDA withdraw the provision, arguing that dietary supplements are often useful in providing nutritional support to complement drug therapy or medical treatment and that the agency should encourage such information to be communicated to consumers. One comment stated that as long as the statement makes it clear that the product is being recommended for its nutritional impact on structure or function "as part of the therapy and not as the therapy itself," FDA should permit the statement. According to the comment, "use as part of your diet when taking insulin to help maintain a healthy blood sugar level" should be acceptable because the product is being recommended for its nutritional impact on structure or function as part of the

therapy and not as the therapy itself. Another comment asked whether removing the words "when taking insulin" from the statement would make it an acceptable structure/function claim.

The agency agrees that dietary supplements may be useful in providing nutritional support. Associating such a statement with an express or implied claim that the dietary supplement augments a therapy or drug action, however, implies that the dietary supplement has a role in treating or preventing the disease for which the drug or other therapy is used.

The agency does not agree that the proposed claim involving insulin is an acceptable structure/function claim. Persons who take insulin have a disease, namely, diabetes. By referring to the use of the dietary supplement in conjunction with and for the same purpose ("to maintain a healthy blood sugar level") as a drug (insulin), which is used to for a disease (diabetes), the statement implies that the dietary supplement will help treat diabetes.

A general statement that a dietary supplement provides nutritional support would be an acceptable structure/function claim, provided that the statement does not suggest that the supplement is intended to augment or have the same purpose as a specific drug, drug action, or therapy for a disease. In the example, if the statement were changed to "use as part of your diet to help maintain a healthy blood sugar level," the claim

would be considered acceptable. Deleting the reference to the drug, insulin, would remove the implication that the dietary supplement is used to augment the insulin to treat, mitigate, prevent, or cure diabetes.

On its own initiative, FDA is modifying § 101.93(g)(2)(vii) to limit its applicability to claims for augmentation of drugs or therapies that are intended to diagnose, mitigate, treat, cure, or prevent disease.

(76.) Another comment noted that the agency did not address the use of synonyms for "augment," such as "strengthen," "reduce," "improve," "modify," "inhibit," "protect," or "defend."

Use of these terms may be appropriate in some contexts, i.e., when the statements do not suggest disease prevention or treatment use. If, however, the use of these terms implies that the dietary supplement augments a particular therapy or drug action or otherwise suggests an effect on disease, the agency will consider the statement a disease claim.

(77.) A trade association maintained that under the proposal, bread, crackers, and other baked goods used in conjunction with prescription drugs and/or other therapy would not be considered a food, but a drug, under certain circumstances.

Section 101.93 is intended to provide regulatory criteria for statements made for dietary supplements. Under section 201(ff)(2)(B) of the act, a dietary supplement does not include a

product represented for use as a conventional food or as a sole item of a meal or the diet. If statements made for breads, crackers, and other baked goods characterize the relationship between a substance in the food and a disease or health-related condition, they must comply with the health claims provisions for foods under section 403(r)(1)(B) and (r)(3) through (r)(4) of the act.

Q. Role in Body's Response to Disease or Disease Vector (§ 101.93(g)(2)(viii))

Under proposed § 101.93(g)(2)(viii), a statement would have been considered a disease claim if it explicitly or implicitly claimed a role in the body's response to a disease or to a vector of disease. The preamble to the proposal defined a vector of disease as an organism or object that is able to transport or transmit to humans an agent, such as a virus or bacterium, that is capable of causing disease in man. The preamble offered as examples of disease claims under this criterion claims that a product "supports the body's antiviral capabilities" or "supports the body's ability to resist infection." A more general reference to an effect on a body system that did not imply prevention or treatment of a disease state would not have constituted a disease claim under this criterion. FDA provided as an example of an acceptable structure/function claim under this criterion "supports the immune system."

(78.) Two comments from health associations supported this provision. One comment from a manufacturer argued that it should be deleted because a number of nutrients and dietary supplements "have a role in the body's response to disease." One comment argued that the body has natural defenses to disease, that these are normal functions of the body, and that therefore, statements such as "enhances disease resistance" should be allowable as structure/function claims. Comments from a consumer organization and a member of the President's Commission on Dietary Supplement Labels asserted that the provision made too many claims allowable. These comments stated that as long as a claim includes a disease-fighting function of the body, e.g., "supports the immune system," it should be considered a disease claim, regardless of other functions that might be involved.

FDA agrees that nutrients and dietary supplements may play a role in the body's response to disease. This does not mean, however, that disease prevention claims are acceptable structure/function claims. The act requires dietary supplement manufacturers who wish to make disease prevention claims to do so by obtaining authorization for a health claim or by obtaining new drug approval. Although FDA agrees that claims that a product fights disease, or enhances disease-fighting functions of the body, are disease claims, FDA does not agree that claims such as

"supports the immune system" are specific enough to imply prevention of disease.

(79.) Several comments argued that there was no significant difference between "supports the immune system" (identified as a structure/function claim in the proposal) and "supports the body's antiviral capabilities" (identified as a disease claim in the proposal). One view was that both should be considered structure/function claims. Conversely, other comments contended that "supports the immune system" is a disease claim, because it could be interpreted as a claim for treatment or prevention of human immunodeficiency virus (HIV) disease. Another comment recommended that "supports the body's antiviral capabilities" be allowable as a structure/function claim, stating that the broader "supports the immune system" statement was vague and useless to consumers because the immune system has many functions.

The distinction between the two claims is one of specificity. An intact immune system has several functions. In addition to their role in the defense against pathogens, certain components of the immune system, namely white blood cells, have other important functions. For example, white blood cells play an essential role in the phagocytosis and disposal of aging red blood cells or otherwise damaged cells. A statement of support for the immune system, by itself, conveys no specific reference to disease treatment or prevention. The claim that vitamin A is

necessary to maintaining a healthy immune response does not imply that a specific disease or class of diseases will be prevented. In contrast, a claim that a product "supports the body's antiviral capabilities" represents a claim of treatment or prevention of a specific class of diseases, those caused by viruses (e.g., colds, hepatitis, or HIV infection).

R. Treatment/Prevention of Adverse Events (§ 101.93(g)(2)(ix))

Under proposed § 101.93(g)(2)(ix), a statement would have been considered a disease claim if it explicitly or implicitly claimed to treat, prevent, or mitigate adverse events associated with a therapy for a disease (e.g., "reduces nausea associated with chemotherapy," "helps avoid diarrhea associated with antibiotic use," and "to aid patients with reduced or compromised immune function, such as patients undergoing chemotherapy"). A claim that did not mention a therapy for disease (e.g., "helps maintain healthy intestinal flora") would not have constituted a disease claim under this criterion.

(80.) Comments from two large health organizations supported this provision, while two large business organizations and several other comments criticized it. Those opposing the provision argued that the proposal incorrectly categorized adverse reactions as diseases. Opposing comments also contended that dietary supplements may be useful as an adjunct to therapy by counterbalancing the effects of a drug in depleting a nutrient

or interfering with the metabolism of a nutrient, and that this should be considered a structure/function role.

FDA believes that some of these comments may have misconstrued the provision. The criterion is not intended to capture every adverse event claim, but only claims about adverse events that satisfy the definition of disease. In the proposed rule, this limitation was conveyed by the phrase "and manifested by a characteristic set of signs or symptoms." Because the final rule uses a different definition of disease, § 101.93(g)(2)(ix) has been revised to state that claims about adverse events are disease claims only "if the adverse events constitute diseases." FDA believes that a claim that a product is useful because it counterbalances the effects of a drug in depleting a nutrient or interfering with the metabolism of a nutrient would be acceptable as a structure/function statement. Such a claim would not suggest treatment of an adverse reaction that meets the definition of disease. However, as discussed above, if the claim expressly or impliedly suggests that the supplement is intended to augment a specific drug, drug action, or therapy for a disease, or serve the same purpose as a specific drug or therapy for a disease, then the statement may be considered a disease claim.

(81.) A dietary supplement manufacturer requested that FDA clarify why a statement that refers to a drug but not a disease,

such as "helps individuals using antibiotics to maintain normal intestinal flora" is a disease claim, but a general statement, such as "helps maintain intestinal flora" is a permissible structure/function claim.

Although the statement "helps individuals using antibiotics to maintain normal intestinal flora" does not explicitly refer to a disease, there is an implicit claim that use of the dietary supplement while taking antibiotics will prevent or mitigate a disease. Persons using certain antibiotics are at risk of developing overgrowth in the gut of a pathogenic organism because along with fighting the target organisms in the body the antibiotic can suppress normal intestinal flora that are used to prevent infection in the intestinal tract. A firm that markets its product to address this concern, with claims that the product can be used to maintain normal intestinal flora while taking antibiotics, is making an implied disease prevention claim. Conversely, the statement "helps maintain intestinal flora" alone, without any reference to a disease, drug, drug action, or therapy, does not imply an effect on disease and would be considered a structure/function claim about general health maintenance.

S. Otherwise Affects Disease (§ 101.93(g)(2)(x))

Under proposed § 101.93(g)(2)(x), a statement would have been considered a disease claim if it suggested an effect on a

disease or class of diseases in a manner other than those specifically enumerated in the first nine criteria.

(82.) A food manufacturers' trade association commented that this provision is of no regulatory importance, whereas a dietary supplement trade association and several other comments considered it an over-reaching "catch-all" provision that would allow FDA to treat any claim as a disease claim. These comments provided examples of a number of claims that they believed would be disease claims under this provision, e.g. "provides nutritional support for women during premenstruation by promoting proper fluid balances and breast health," and "ginger supports the cardiovascular system by inhibiting leukotriene and thromboxane synthesis, substances associated with platelet aggregation."

FDA believes that this provision is necessary to allow for implied disease claims that may not fit into the nine enumerated criteria. The nine criteria are examples, and not an exhaustive list, of types of claims that the agency believes would constitute disease claims, based on past experience. Rather than attempting to evaluate or categorize statements that have not yet been presented to FDA, § 101.93(g)(2)(x) recognizes the possibility that other types of statements may also imply disease treatment or prevention. FDA does not believe that the provision will cause the agency to classify any structure/function

statement as a disease claim. To regulate a statement as a disease claim under this provision, the agency would have to show that the statement implied an effect on disease. The two examples quoted in the comments do not appear to the agency to constitute disease claims.

T. Specific Claims Not Mentioned in the Proposed Rule

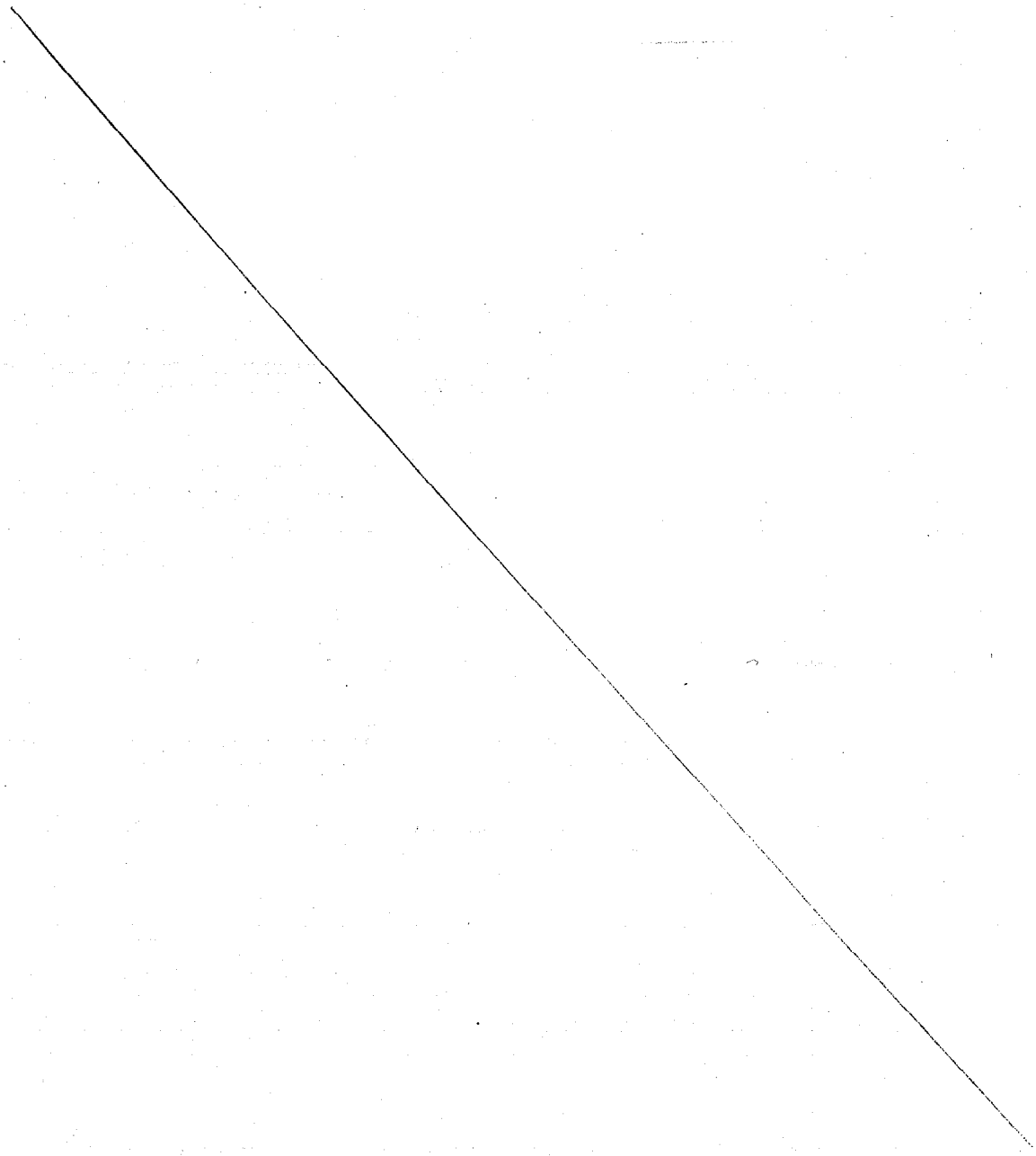
(83.) One comment contended that a dietary supplement called "pain free" or "pain product," that is labeled "to support and maintain joints," should not be regulated as an internal analgesic drug product under the OTC drug review because it is intended to maintain or support "normal well-being and pain levels." According to this comment, however, products sold as "pain relief" or "otherwise indicated to relieve temporary occurrences of arthritis pain" could be regulated as drug products under the OTC review, because the tentative final monograph for internal analgesics requires that such products be labeled for the "temporary relief of minor aches and pains" (53 FR 46204). At the same time, this comment argued that pain, in and of itself, is not a disease and therefore that pain claims should not be regulated as disease claims unless accompanied by an explicit reference to a specific disease.

FDA agrees in part and disagrees in part with this comment. FDA agrees that some minor pain relief claims may be appropriate structure/function claims for dietary supplements. A claim that a product is intended to treat minor pain, without reference to any other conditions, symptoms, or parts of the body that would imply disease treatment or prevention, would be an appropriate strtucture/function claim, because minor pain, by itself, can be caused by a variety of conditions, not all of them disease-related.

FDA does not agree, however, that general well-being or health maintenance claims would encompass such pain claims. Pain is not a normal state, nor are there "normal pain levels." The claim is thus clearly one of pain treatment or prevention. FDA also does not agree that section 403(r)(6) of the act authorizes a product whose name promises freedom from or relief of pain ("pain-free" or "pain product") and whose labeling includes claims related to maintenance or support of joints. While the latter claims alone are appropriate structure/function statements, in conjunction with a name that includes the term "pain," the product is clearly making a claim related to treatment or prevention of joint pain. As explained elsewhere in this document, joint pain is a characteristic symptom of arthritis, and joint pain claims are therefore disease claims. Acceptable structure/function claims could be made, however, for pain associated with nondisease states, e.g., muscle pain following exercise.

(84.) One comment listed several claims and sought concurrence that they were acceptable structure/function claims: "Boosts stamina, helps increase muscle size, and helps enhance muscle tone"; "deters bacteria from adhering to the wall of the

bladder and urinary tract"; and "dietary support during the cold and flu season." Another comment asked whether "promotes general well-being during the cold and flu season" is a permissible claim.



FDA agrees that "boosts stamina, helps increase muscle size, and helps enhance muscle tone" are acceptable structure/function claims, because they do not refer to any disease. However, the agency notes that a claim to increase muscle size implies an effect that may subject the product regulation as an anabolic steroid under the Controlled Substances Act (see 21 U.S.C. 802(41)). "Deters bacteria from adhering to the wall of the bladder and urinary tract" is not an acceptable structure/function claim because it implies prevention of bacterial infections of the bladder and urinary tract. The claims "dietary support during the cold and flu season" and "promotes general well-being during the cold and flu season" are disease claims because they imply that the product will prevent colds and flu or will mitigate the symptoms of those diseases.

(85.) One comment asked that the FDA clarify that dietary supplements can bear "smoking-alternative" claims if they avoid references to nicotine, nicotine withdrawal symptoms, and tobacco-related disease. The comment sought concurrence that the following types of claims were permitted: "Smoking alternative," "temporarily reduces your desire to smoke," "to be used as a dietary adjunct in conjunction with your smoking cessation plan;" and "mimics the oral sensations of cigarette smoke."

FDA agrees that certain smoking alternative claims may be acceptable structure/function claims, if they do not imply

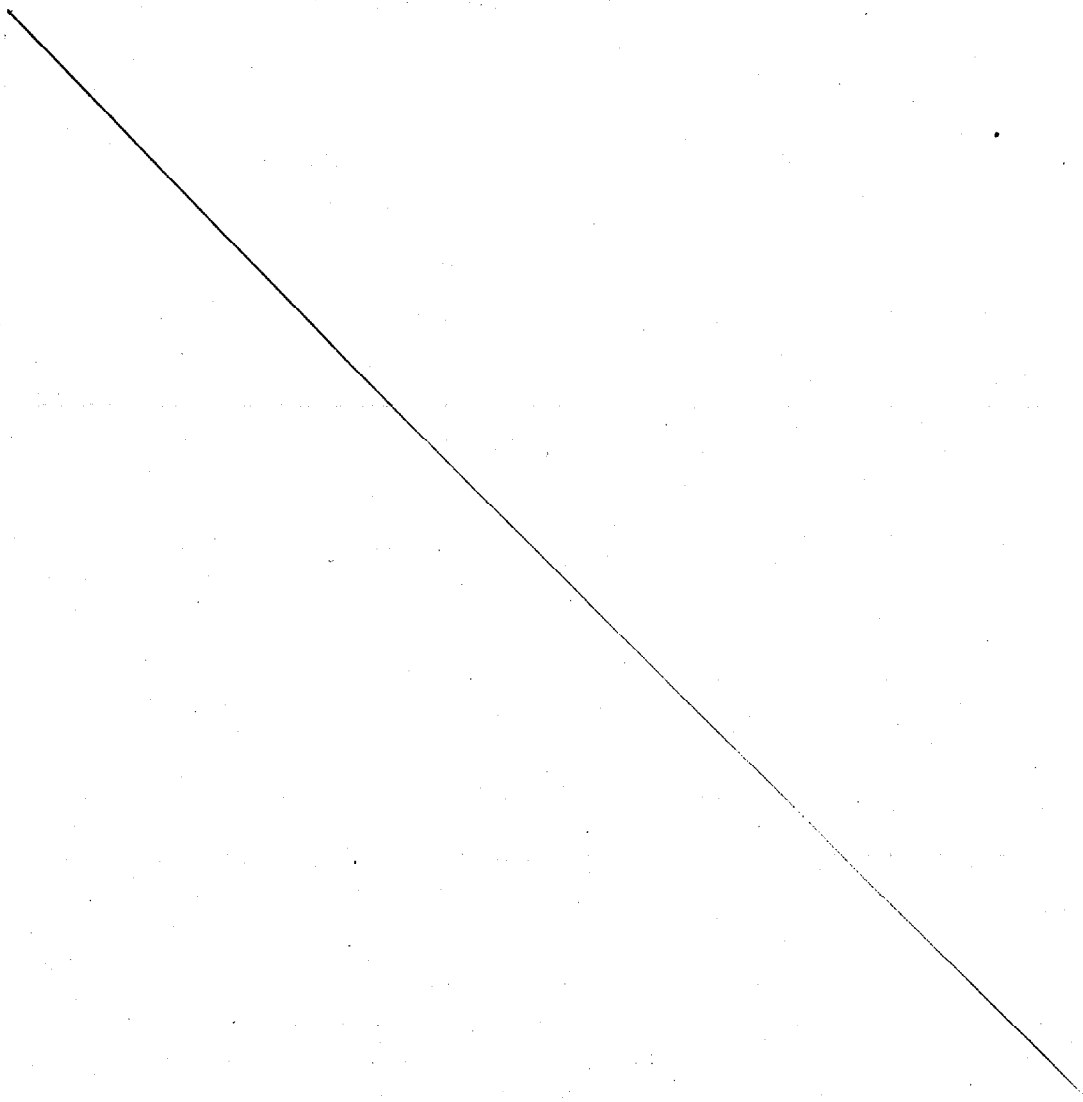
treatment of nicotine addiction, relief of nicotine withdrawal symptoms, or prevention or mitigation of tobacco-related illnesses. "Smoking alternative," "temporarily reduces your desire to smoke" and "mimics the oral sensations of cigarette smoke" may be acceptable (for products that otherwise meet the definition of a dietary supplement), if the context does not imply treatment of nicotine addiction, e.g., by suggesting that the product can be used in smoking cessation, or prevention or mitigation of tobacco-related diseases. For example, such claims would not be disease claims if the context made clear that they were for short-term use in situations where smoke is prohibited or socially unacceptable. "To be used as a dietary adjunct in conjunction with your smoking cessation plan," however, is a disease claim because it is a claim that the product aids in smoking cessation, thereby implying that the product is useful in treating nicotine addiction. As noted earlier, a claim that the product is useful in counterbalancing the effects of a drug in depleting a nutrient or interfering with the metabolism of a nutrient would be acceptable as a structure/function statement.

(86.) One comment offered as acceptable structure/function claims a long list of OTC drug claims provided for in the monographs for antacids, antiflatulents (antigas), antiemetics, nighttime sleep-aids, stimulants (alertness aids), daytime sedatives, aphrodisiacs, products for relief of symptoms of

benign prostatic hypertrophy, anticholinergics (products that, at low doses, depress salivary and bronchial secretions), and products for certain uses. Two comments sought clarification that inclusion of a claim in an OTC monograph does not preclude its use as a structure/function claim.

FDA agrees that some of the claims on the comment's list of OTC drug claims may be acceptable structure/function claims, but believes that others on the list are disease claims. Of the claims listed in the comment from the "Antacids" monograph, "relief of sour stomach" and "upset stomach" are acceptable structure/function claims, because they refer to a nonspecific group of conditions that have a variety of causes, many of which are not disease-related. Thus, they are not characteristic of a specific disease or class of diseases. Although "relief of heartburn" and "relief of acid indigestion" without further qualification are not appropriate structure/function claims, the agency has concluded that "occassional heartburn" and "occassional acid ingestion" can also be considered nonspecific symptoms, arising as they do in overindulgence and other sporadic situations. These claims could be appropriate structure/function claims. In contrast, "recurrent" or "persistent" heartburn and acid indigestion can be hallmarks of significant illness, and are therefore disease claims.

All of the claims listed in the comment from the "Antiflatulents" (antigas) monograph are acceptable structure/function claims, because the symptoms in the claims are not sufficiently characteristic of specific diseases: "Alleviates the symptoms referred to as gas," "alleviates bloating," "alleviates pressure," "alleviates fullness," and "alleviates stuffed feeling." The claim listed in the comment



from the "Antiemetics" monograph, "for the prevention and treatment of the nausea, vomiting, or dizziness associated with motion," is also a permitted structure/function claim.

Of the claims listed in the comment from the "Nighttime" sleep-aids monograph, "for the relief of occasional sleeplessness" is an acceptable structure/function claim, because occasional sleeplessness is not a characteristic symptom of a disease. "Helps you fall asleep if you have difficulty falling asleep," and "helps to reduce difficulty falling asleep" are disease claims because, unless the context makes clear that the product is only for occasional sleeplessness, they imply treatment of insomnia, a disease. The claim listed in the comment from the "Stimulants" (alertness aids) monograph, "helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness," is an acceptable structure/function claim because occasional fatigue and drowsiness are not characteristic symptoms of a specific disease or class of diseases. FDA notes, however, that chronic fatigue or daytime drowsiness can be symptoms of chronic fatigue syndrome and narcolepsy, respectively. Products labeled "to help restore mental alertness or wakefulness when experiencing fatigue or drowsiness" should not imply treatment of either of these diseases.

Of the claims listed in the comment from the "Daytime" sedatives monograph, almost all are acceptable structure/function

claims. "Occasional simple nervous tension," "nervousness due to common every day overwork and fatigue," "a relaxed feeling," "calming down and relaxing," "gently soothe away the tension," "calmative," "resolving that irritability that ruins your day," "helps you relax," "restlessness," "nervous irritability," and "when you're under occasional stress, helps you work relaxed" are all acceptable structure/function claims, because all suggest occasional rather than long-term or chronic mood changes. Although occasional or acute symptoms can be characteristic of diseases in other settings, none of the occasional symptoms referred to here is characteristic of a specific disease. "Nervous tension headache" is a disease claim because tension headache meets the definition of a disease.

Of the claims listed in the comment from the "Aphrodisiacs" monograph, "arouses or increases sexual desire and improves sexual performance" is an acceptable structure/function claim because it does not imply treatment of a disease. "Helps restore sexual vigor, potency, and performance," "improves performance, staying power, and sexual potency," and "builds virility and sexual potency" are disease claims because they use the term "potency," which implies treatment of impotence, a disease. If, however, these claims made clear that they were intended solely for decreased sexual function associated with aging, they could be acceptable structure/function claims. The claim from the

"Products for relief of symptoms of benign prostatic hypertrophy" monograph ("To relieve the symptoms of benign prostatic hypertrophy, e.g., urinary urgency and frequency, excessive urinating at night, and delayed urination") is a disease claim, because benign prostatic hypertrophy meets the definition of a disease.

The claim listed in the comment from the "Anticholinergics" monograph is a disease claim. "Relieve excessive secretions of the nose and eyes" refers to the characteristic signs or symptoms of hay fever. Of the claims listed in the comment from the "Products for certain uses" monograph, "digestive aid," "stool softener," "weight control," and "menstrual" are, by themselves, acceptable structure/function claims if the labeling does not otherwise imply treatment or prevention of a disease. None mentions a characteristic symptom of a disease. "Laxative" is a not a disease claim, if the labeling makes clear that the intended use is for treatment of occasional rather than chronic constipation. "Nasal decongestant," "expectorant," and "bronchodilator" are disease claims. "Nasal decongestant" is a treatment for a characteristic symptom of colds, flu, and hay fever. "Expectorant" is a treatment for a characteristic symptom of colds, flu, and bronchitis. "Bronchodilator" is a treatment for bronchospasm, a characteristic symptom of asthma.

The claim from the "Products for the treatment and/or prevention of nocturnal leg muscle cramps" monograph ("treatment and/or prevention of nocturnal leg muscle cramps, i.e., a condition of localized pain in the lower extremities usually occurring in middle life and beyond with no regular pattern concerning time or severity") is an appropriate structure function claim. Nocturnal leg cramps do not meet the definition of disease.

As is clear from this response, FDA agrees that inclusion of a claim in an OTC monograph does not preclude its use as a structure/function claim. FDA notes, however, that in light of the statutory requirement that dietary supplements bear all information that is material in light of consequences that may result from use of the product or representations made about it, dietary supplements that contain or are labeled as containing ingredients covered by an OTC monograph and that are being sold for the claims covered by the monograph may be misbranded to the extent that they omit material information required under the monograph. For example, if the OTC monograph required a label statement that products containing a particular ingredient should not be used by persons taking a prescription monoamine oxidase

inhibitor, a dietary supplement containing that ingredient would be misbranded if its label did not include such statement.

U. Substantiation of Claims

(87.) Several comments requested that the final rule explicitly state that structure/function statements must be adequately substantiated and that FDA provide guidance on what constitutes adequate substantiation. One comment maintained that adequate substantiation is critical to ensuring that consumers receive truthful and accurate information about the benefits of dietary supplements. Another comment argued that this final rule should focus on adequate substantiation of claims rather than on delineating the boundaries between structure/function claims and disease claims. Other comments maintained that substantiation is not as effective in preventing consumer fraud as preapproval of the claims because consumers will be using the products long before the label claims are investigated.

FDA agrees that the statutory requirement to substantiate claims is important. FDA does not agree, however, that it is necessary to state in the regulatory text of the final rule that structure/function claims must be adequately substantiated. Section 101.93(a)(3) requires a firm notifying FDA of a claim under section 403(r)(6) of the act to certify that the firm has substantiation that the claim is truthful and not misleading. FDA also does not agree that substantiation is an appropriate

alternative to distinguishing structure/function claims from disease claims. The requirement that structure/function statements and other statements for dietary supplements under section 403(r)(6) of the act be adequately substantiated is distinct from the requirement that such statements not claim to diagnose, treat, mitigate, cure, or prevent disease. Both of these requirements are imposed by the statute and must be complied with.

(88.) Several comments offered advice on what types of evidence should constitute adequate substantiation. A consumer health organization suggested that health claims and structure/function claims for dietary supplements be based on the totality of the publicly available scientific evidence, including results from well-designed studies conducted in a manner consistent with generally recognized scientific principles and procedures. The comment added that consumers would be better served if standards for support applied to both health claims and structure/function claims. Another consumer health organization suggested that substantiation be based on "significant scientific agreement."

Many of the comments suggested that the agency adopt FTC standards for substantiation. A comment from FTC explained that FTC typically applies a substantiation standard known as "competent and reliable scientific evidence" to claims about the

safety and effectiveness of dietary supplements, after first looking at the overall context to determine what the claim is. The comment further stated that FTC's approach to substantiation is consistent with the guidance provided by the President's Commission on Dietary Supplement Labels, and, because FDA concurred with the Commission's guidance on substantiation, the comment suggested that FDA refer to the Commission guidance in the final rule.

As stated above, the agency does not believe that this final rule is the appropriate venue to address the substantiation requirement. FDA does, however, agree that claims under section 403(r)(6) of the act should be supported by adequate scientific evidence and may provide additional guidance regarding substantiation for 403(r)(6) statements at a future date.

The Commission report included guidance on what quantity and quality of evidence should be used to substantiate claims made under 403(r)(6) of the act. It also contained guidance on the content of the substantiation files for such statements, including the 30-day notification letter to FDA, identification of the product's ingredients, evidence to substantiate the statements, evidence to substantiate safety, assurances that good manufacturing practices were followed, and the qualifications of the person(s) who reviewed the data on safety and efficacy. In a notice published in the FEDERAL REGISTER (63 FR 23624 at 23633),

FDA stated that it agreed with the guidance of the Commission. FDA encourages manufacturers of dietary supplements making a 403(r)(6) of the act statement for a dietary supplement to follow this guidance.

(89.) A food manufacturer suggested that the agency require dietary supplement manufacturers making structure/function claims to disclose in labeling any and all scientific studies supporting the claim. In addition, the comment advocated requiring that these studies be performed using the marketed formulation. The comment also urged FDA to determine how contrary studies should be addressed.

DSHEA does not require dietary supplement labeling that carries a statement under section 403(r)(6) of the act to include in the labeling "any and all scientific studies supporting the claim." Section 403(r)(6)(B) of the act requires only that the "manufacturer have substantiation that such statement is truthful and not misleading." Contrary studies should be considered when deciding whether to make and how to word a 403(r)(6) of the act statement to ensure that any statements made are truthful and not misleading. Additionally, in response to a request for substantiation for the statement, the agency would expect manufacturers to provide a requester with contrary as well as supporting studies.

There is no specific statutory requirement that the studies substantiating the statement be performed using the actual marketed formulation. However, many ingredients and factors influencing the formulation can affect the safety and effectiveness of the dietary supplement. These variations from the marketed product should be considered before using a study to substantiate a statement made for a particular product.

V. Enforcement Issues

(90.) One comment said that the proposal shifts the burden of proof to manufacturers to show that their files match and support the claims made for their products.

The regulations issued by this final rule do not address or affect the burden of proof during enforcement actions. However, section 403(r)(6)(B) of the act clearly states that manufacturers must have substantiation to show that the statements that they make under section 403(r)(6) of the act are truthful and not misleading. This indicates that manufacturers must be prepared to demonstrate to the court that they have support for each claim.

(91.) One comment predicted widespread noncompliance with the rule because of its complexity and limited FDA resources.

FDA disagrees with the comment. FDA believes that most of the rule is straightforward, and the comments received on the proposed rule indicate that dietary supplement manufacturers

understood the provisions of the rule. Moreover, as noted in the Analysis of Impact in section VI.E of this document, most of the claims of which FDA has been notified are consistent with the final rule. Thus, based on what has been provided to FDA, most manufacturers would appear to be already in compliance with this final rule. If it becomes apparent that there are provisions that are being violated because of true confusion about their applicability, FDA will issue clarifying guidance. FDA agrees that its enforcement resources are limited, and is issuing this rule in part to avoid inefficient use of those resources on case-by-case enforcement. FDA believes that the dietary supplement industry will make good faith efforts to comply with this rule, once it becomes effective.

W. Other Comments

(92.) One comment said FDA should conduct an educational campaign to enhance public awareness of the differences between structure/function claims and disease claims and the meaning of individual claims.

FDA intends to conduct various outreach activities on dietary supplement matters.

(93.) One comment said FDA should amend the tentative final monograph on OTC laxatives to be consistent with the rule. The comment explained that the tentative final monograph should permit the words "help maintain regularity" on OTC labeling.

The agency disagrees with the comment. The fact that "helps maintain regularity" is an acceptable structure/function claim does not mean that it satisfies the requirements for inclusion in an OTC monograph, including the requirement of a finding of general recognition of safety and effectiveness.

(94.) Several comments addressed manufacturing or related issues. One comment said FDA should investigate effects of dissolution on product potency and efficacy, while other comments advocated using United States Pharmacopeia standards for all dietary supplements on matters pertaining to dissolution, disintegration, purity, and potency. One comment added that poor product quality would present a health threat to consumers and result in economic fraud.

Another comment said FDA should concentrate on standardization and quality control instead of regulating labeling statements, but offered no specific suggestions. Some comments, however, made specific recommendations. One comment said that product labels should contain lot numbers and expiration dates and that manufacturers should conduct stability tests to determine accurate expiration dates. Another comment said the public should be protected against poor manufacturing standards for herbal products. Other comments simply stated that there is substantial potential for public harm because there are: Multiple sources of dietary supplement ingredients; multiple

suppliers; a lack of regulatory production standards, or questions concerning product safety, efficacy, and manufacturing quality; vigorous product promotion; and a sizeable market. One comment simply asked for good manufacturing practice regulations for dietary supplements.

Manufacturing issues are outside the scope of this rule. FDA intends to issue a separate proposed rule on current good manufacturing practice (CGMP) for dietary supplements, and that proposed CGMP rule may address some of the issues raised by the comments.

III. Legal Authority

A. Scope of Section 403(r)(6) of the Act

1. Relationship Between Sections 403(r)(6) and 201(g)(1)(C) of the Act

(95.) Several comments stated that the proposal mistakenly suggests that there is only one type of structure/function claim that may be used for dietary supplements. Some of these comments said that if a structure/function claim does not trigger drug status for the product and is not a health claim, then such a claim may be made in labeling for a dietary supplement so long as it is truthful and not misleading. These comments asserted that such a claim is not subject to the notice, labeling, or disclaimer requirements in section 403(r)(6) of the act. As an example, the comments said the claim that "calcium helps build

strong bones" is not a health claim because it does not characterize a relationship between the substance and a disease, damage, or dysfunction of the body. The comments added that FDA recognized this in the final rule that it published in the FEDERAL REGISTER on September 23, 1997 (62 FR 49859, 49860, 49863, and 49864), when it stated in the preamble that claims that cranberry juice cocktail helps maintain urinary tract health or that calcium builds strong bones and teeth are not health claims because no disease is mentioned explicitly or implicitly. Some comments added that FDA cannot say that only those claims falling under section 406(r)(6) of the act are structure/function claims because such a result would be contrary to the act and would mean that the proposed rule must be withdrawn.

FDA agrees with these comments in part and disagrees in part. The agency agrees that statements such as "calcium helps build strong bones" are not health claims because they do not characterize the relationship between a substance and a disease or health-related condition. Rather, such statements are structure/function claims authorized by section 403(r)(6) of the act.

FDA does not agree with the comment's statement that dietary supplements may bear structure/function claims without complying with the notice, disclaimer, and other requirements of section 403(r)(6) of the act. Section 403(r)(6) of the act, by its

terms, applies to dietary supplements. The other possible source of authority to make structure/function claims on dietary supplements is section 201(g)(1)(C) of the act, which provides that "articles (other than food) intended to affect the structure or any function of the body of man or other animals" are drugs. Under this provision, foods may make claims to affect the structure or function of the body without being regulated as drugs. By its terms, however, section 201(g)(1)(C) of the act exempts a dietary supplement that bears a structure/function claim from drug regulation only if it is also a food. The last sentence of section 201(ff) of the act provides, "Except for purposes of section 201(g), a dietary supplement shall be deemed to be a food within the meaning of this Act." The clear import of this language is that dietary supplements are not foods under section 201(g) of the act and therefore cannot qualify for the "(other than food)" exception to the drug definition in section 201(g)(1)(C). As a result, dietary supplements that use structure/function claims may do so only under section 403(r)(6) of the act and are therefore subject to the disclaimer, notification, and other requirements in that section and in FDA's implementing regulation.

The agency acknowledges that it took a contrary position in the September 1997 final rule preamble referred to in the comment. In that preamble, FDA said that a dietary supplement

could bear a structure/function claim under the "(other than food)" exception to the definition of "drug" in section 201(g)(1)(C) of the act, provided that the claim was truthful, non-misleading, and derived from nutritive value (see 62 FR 49859 at 49860, 49863, and 49864). However, the agency has now reconsidered in light of the plain language of section 201(ff) of the act and is revoking its statements on this subject in the September 1997 preamble (i.e., the statements at 62 FR 49859 at 49860, 49863, and 49864 concerning structure/function claims for dietary supplements under section 201(g)(1)(C)). It should be noted, however, that the agency is not revoking its statements in that preamble concerning structure/function claims for conventional foods under section 201(g)(1)(C) of the act. As explained in the September 1997 preamble (62 FR 49859 at 49860), conventional foods may make structure/function claims under section 201(g)(1)(C) of the act as long as such claims are truthful, non-misleading, and derive from the nutritive value of the food.

For a limited transition period, FDA does not intend to take enforcement action against firms who have relied on the agency's September 1997 final rule preamble statements to make a structure/function claim for a dietary supplement under section 201(g)(1)(C) of the act. To allow a reasonable time for the necessary label changes, the transition period will last until

the applicable compliance date for the rest of the rule; i.e., small businesses will have 18 months from publication to comply, and other firms will have 12 months. As of the applicable compliance date, firms that have been making structure/function claims under section 201(g)(1)(C) of the act must either remove the claim or comply with the requirements of section 403(r)(6) of the act and § 101.93, including notifying FDA of the claim and relabeling to add the required disclaimer. New structure/function claims are not subject to this transition period; any firm that makes a structure/function claim in the labeling of a dietary supplement after the effective date of this rule must comply with section 403(r)(6) of the act and § 101.93.

(96.) One comment objected to a sentence in the introductory paragraph in the preamble to the proposed rule. The sentence stated that, before DSHEA, certain claims could have rendered a product a "drug" under the act. The comment argued that even before DSHEA, dietary supplements could make structure/function claims and not be considered drugs. The comment said that section 201(g)(1)(C) of the act expressly excluded food from the definition of drug and that dietary supplements fell within the "food" exception. The comment characterized DSHEA as limiting and restricting "what had been the unconditional right of dietary supplement marketers to make structure/function claims."

The agency agrees that before DSHEA, dietary supplements that were also foods could make structure/function claims under section 201(g)(1)(C) of the act without being considered drugs. However, the passage of DSHEA changed the regulatory framework for structure/function claims on dietary supplements by adding sections 201(ff) and 403(r)(6) to the act. As explained in the response to the preceding set of comments, section 201(ff) of the act provides that dietary supplements are not considered food for purposes of section 201(g). Therefore, dietary supplements may no longer make structure/function claims under the "food" exception to the drug definition in section 201(g)(1)(C) of the act. FDA therefore agrees with the comment that in one respect, DSHEA limited the ability of dietary supplement marketers to make structure/function claims.

The sentence in the introductory paragraph of the preamble to the proposed rule correctly stated that "certain claims"--structure/function claims for dietary supplements that were not also foods--could have rendered the product a drug before the passage of DSHEA (63 FR 23624). Post-DSHEA, however, dietary supplements may make structure/function claims under section 403(r)(6) of the act regardless of whether they are also foods. Thus, although in one way DSHEA did limit the ability of dietary supplement marketers to make structure/function claims, it also significantly expanded the opportunity to make structure/function

claims in another way by removing the limitation that dietary supplements must be foods to make structure/function claims. Under section 403(r)(6) of the act, claims may be made for nondisease effects of a dietary supplement on the structure or function of the body, regardless of whether those effects are nutritive, as long as the product is intended to supplement the diet as provided in section 201(ff)(1) of the act.

2. Structure/Function Claims for Conventional Foods

(97.) Several comments sought consistency in the treatment of conventional foods and dietary supplements with respect to structure/function claims and health claims. Some of these comments contended that this rule would permit dietary supplements to carry claims that would be health claims if made for a conventional food. One comment stated that differential treatment of foods and dietary supplements was inconsistent with the Commission's recommendations. This comment suggested that differential treatment would cause consumers to perceive dietary supplements as better sources for safeguarding health than conventional foods. One comment expressed the view that the rule should apply to claims for conventional foods as well as dietary supplements and requested FDA to clarify the rule's scope. Other comments said that any structure/function claims that may be made for dietary supplements may also be made for conventional foods. The comments explained that the history of the act shows that

claims that food affect the structure or function of the body do not result in the food being classified as a drug, citing the district court and appellate decisions in American Health Products Co. v. Hayes, 574 F. Supp. 1498, 1501 (S.D.N.Y. 1983), aff'd, 744 F.2d 912 (2d Cir. 1984). Another comment stated that established case law shows that an article may be a food if it is used primarily for taste, aroma, or nutritional value, but that nutritional value is not required in all instances. One comment further noted that FDA, when it implemented the labeling requirements for DSHEA (62 FR 49859, 49860, and 49861) said that it was committed to "as much parity between dietary supplements and conventional foods as is possible within the statute" and that FDA has recognized that a dietary supplement may lawfully be in conventional food form, but must be represented as a dietary supplement (citing 62 FR 49826 at 49837, September 23, 1997).

Given this background, the comments argued that FDA cannot take the position that a structure/function claim may be made for a conventional food only if the effect derives from the food's nutritional value. One comment added that the act does not distinguish foods based on their nutritional value and that DSHEA considers structure/function claims for all dietary ingredients to be "statements of nutritional support." The comment said FDA, therefore, should recognize that structure/function claims that can be made for dietary ingredients when those ingredients are in

dietary supplements can also be made when those ingredients are in conventional food, but added that the disclaimer statement and notification to FDA, as required by section 403(r)(6)(C) of the act, apply only to dietary supplements and not to conventional food. One comment said that requiring structure/function claims for conventional foods to be derived from the food's nutritional value would create a marketing disparity and put conventional foods at a competitive disadvantage.

This rule applies to claims for dietary supplements only. Its purpose is to implement section 403(r)(6) of the act, which applies to dietary supplements only. Therefore, a detailed discussion of the regulatory framework applicable to structure/function claims for conventional foods, which are made under section 201(g)(1)(C) of the act, is beyond the scope of the rule. FDA advises, however, that for consistency, the agency is likely to interpret the dividing line between structure/function claims and disease claims in a similar manner for conventional foods as for dietary supplements. The agency also notes that as discussed in the response to comment 1 in section II.A of this document, FDA reaffirms the statements about structure/function claims for conventional foods in the September 23, 1997 (62 FR 49859), final rule entitled "Food Labeling: Nutrient Content Claims, Health Claims, and Statements of Nutritional Support for Dietary Supplements." As explained in that rule (62 FR 49859 at

49860, 49861, and 49864), the fact that structure/function claims for conventional foods are limited to effects derived from nutritional value, while structure/function claims for dietary supplements are not, is a result of differences in the language of the exemption for foods in section 201(g)(1)(C) of the act, as interpreted by the courts (see Nutrilab, Inc. v. Schweiker, 713 F.2d 335, 338 (7th Cir. 1983)), and the language of section 403(r)(6) of the act.

(98.) One comment suggested revising the definition of "disease or health-related condition" in proposed § 101.14(a)(6) to include a reference to § 101.93, and also recommended revising the definition of "health claim" at § 101.14(a)(1) to be consistent with § 101.93. Currently, § 101.14(a)(1) reads as follows:

> Health claim means any claim made on the label or in labeling of a food, including a dietary supplement, that expressly or by implication, including "third party" references, written statements (e.g., a brand name including a term such as "heart"), symbols (e.g., a heart symbol), or vignettes, characterizes the

relationship of any substance to a disease or health-related condition. Implied health claims include those statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between the presence or level of a substance in the food and a disease or health-related condition.

The comment would revise the definition to read as follows:

Health claim means any claim made on the label or in labeling of a food, including a dietary supplement, that expressly or by implication, including "third party" references, written statements (e.g., a brand name that includes or implies a disease, such as "Raynaudin"), symbols, or vignettes, characterizes the relationship of any substance to a

> disease or health-related condition (e.g., disease-indicating electrocardiogram tracings, pictures of organs that suggest prevention or treatment of a disease state, the prescription symbol, or any reference to prescription use). Implied health claims include those statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between the presence or level of a substance in the food and a disease or health-related condition.

As stated in response to comment 51 of section II.I of this document, FDA does not believe that §§ 101.14(a)(1) and 101.93(g) are inconsistent. As a result of the special regime for dietary supplements under DSHEA, there may be some differences in the treatment of dietary supplements and conventional foods under § 101.14(a)(1).

3. Relationship Between Structure/Function Claims and Health Claims

(99.) One comment stated that the proposed rule "improperly distinguishes between other health-related claims and structure/function claims." Relying in part on the introduction to section 403(r)(6) of the act ("For purposes of paragraph (r)(1)(B) * * *"), the comment asserted that structure/function claims are a subset of the claims authorized by section 403(r)(1)(B) of the act (health claims). Consequently, because claims under section 403(r)(1)(B) of the act may characterize the relationship of a nutrient to a disease, the comment stated that FDA cannot preclude structure/function claims from making any contextual references to diseases.

FDA disagrees with this comment. Structure/function claims are not a subset of health claims because, clearly, there are claims about the effect of a product on the structure or function of the body that are not also health claims. To be a health claim, a claim must refer to the relationship between a food substance and a disease or health-related condition. FDA interprets "health-related condition" to mean a state of health leading to disease. Claims such as "calcium builds strong bones" are not health claims because they do not refer explicitly or implicitly to any disease or health-related condition. Therefore, the comment is based on an invalid premise.

(100.) One comment requested that FDA revise § 101.93(f) to state that the requirements of section 403(r)(6) of the act, e.g., use of the disclaimer and substantiation, apply only to structure/function claims that fall within the definition of a "health claim" in § 101.14(a)(1) and (a)(5). According to this comment, the introduction to section 403(r)(6) of the act ("For purposes of paragraph (r)(1)(B) * * *") establishes that structure/function claims that do not fall within the definition of health claims are not subject to section 403(r)(6), and may be made without complying with any of its requirements.

FDA does not agree and, in fact, believes that the opposite is true. As explained elsewhere in this document and in the proposed rule, structure/function claims that fall within the definition of health claims, or that otherwise constitute disease claims, do not fall within the scope of claims authorized under section 403(r)(6) of the act, but other structure/function claims do fall within the scope of section 403(r)(6) and are subject to its requirements. Adopting the interpretation advocated by the comment would bring about illogical results for dietary supplement labeling claims in two ways. First, structure/function claims that are also health claims would not be subject to the health claims prior authorization requirements, but instead could be made simply by meeting the requirements of section 403(r)(6) of the act and FDA's implementing regulations.

The language in section 403(r)(6) of the act excluding claims to affect disease from the coverage of that section demonstrates that Congress made a public health judgment that claims promoting dietary supplements for disease uses should continue to require premarket authorization. It would not make sense for Congress to exclude labeling claims pertaining to disease uses in one part of section 403(r)(6) of the act, while permitting such claims in another paragraph of the same section. Moreover, the interpretation advocated by the comment would lead to confusing and contradictory labeling. A dietary supplement that bears a health claim--a claim that, by definition, is a claim that a substance in the supplement in some way has an effect on a disease--would also have to bear a contradictory disclaimer that it is not intended to treat, mitigate, or prevent any disease. Second, structure/function claims that are not also health claims would not be authorized under section 403(r)(6) of the act at all. In fact, a structure/function claim on a dietary supplement would subject it to drug regulation because, as explained in the response to comment 1 in section II.A of this document, section 403(r)(6) of the act is the only provision that authorizes the use of structure/function claims on dietary supplements.

The introductory language in section 403(r)(6) ("For purposes of [section 403](r)(1)(B) * * *") does not support the interpretation advocated in the comment. If Congress had wanted

to subject only structure/function claims that are also health claims to section 403(r)(6) of the act, it could have done so much more directly by using language such as "A statement for a dietary supplement may be made if * * * and the statement is a statement of the type governed by paragraph (r)(1)(B)." The ambiguity of the "For purposes of (r)(1)(B)" language is well demonstrated by the diametrically opposed interpretations adopted by this comment and the preceding comment. FDA interprets this language as a caution that the category of claims covered by section 403(r)(6) of the act is not to be interpreted as coextensive with health claims, the category covered by section 403(r)(1)(B) of the act. Congress may have been concerned that the health claims category would swallow the category of claims under section 403(r)(6) of the act because all claims under section 403(r)(6) could be characterized as referring to a "health-related condition" if that term were defined broadly as "a state of health." The result would have been that all structure/function claims, as claims about the relationship between a substance and a health-related condition, would also have been health claims and would have required premarket authorization. By including the introductory language, Congress effectively forestalled such an interpretation.

(101.) Another comment said the proposed rule does not distinguish between structure/function statements that assert

health claims and those that do not, and said the failure to make this distinction would mean that more products would be subject to the rule than necessary.

FDA does not agree that the rule fails to distinguish between structure/function claims that do and do not assert health claims. On the contrary, the rule makes clear that only structure/function claims that do not assert health claims may be made under section 403(r)(6) of the act. To the extent that the comment may be suggesting that structure/function claims that are also health claims should be exempt from the health claims authorization requirements, the agency disagrees for the reasons given in the response to the previous comment.

B. Miscellaneous Legal Issues

(102.) Two comments said the proposed rule violated the Administrative Procedure Act because it was arbitrary and capricious, on two grounds. One comment asserted that FDA failed to consider an important aspect of the problem of distinguishing between drug claims and dietary supplement claims: The application of the "general well-being" provision of section 403(r)(6) of the act. The comment argued that FDA should have considered whether claims relating to normal body functions might qualify as "general well-being" claims under section 403(r)(6) of the act before deciding to regulate them as disease claims. The comment also argued that FDA's explanation of the need for the

proposed rule ran counter to the evidence before the agency, in that the agency's actions on notifications of claims under section 403(r)(6) of the act did not support a need for further regulation.

The "general well-being" provision of section 403(r)(6) of the act authorizes statements in dietary supplement labeling that describe "general well-being from consumption of a nutrient or dietary ingredient" (section 403(r)(6)(A) of the act). FDA did not consider whether statements were authorized under this provision in developing the proposed rule because the purpose of the rule was to implement the structure/function provisions of section 403(r)(6)(A) of the act, not other provisions. However, consideration of this provision as applied to normal body functions would not have led to a different result. The criteria in the rule were developed to identify claims that refer directly or indirectly to an effect on disease and do not encompass claims that refer only to general well-being. Claims relating to normal body functions are authorized under the rule.

The comment's argument about the use of FDA's actions on notifications of claims under section 403(r)(6) of the act to justify the rule is addressed in comment 4 of section II.A of this document.

(103.) One comment claimed that the proposal does not require FDA to show any evidence of a manufacturer's intent to find that

a dietary supplement claim constitutes an illegal drug claim. The comment argued that proposed § 101.93(g)(2)(ii), (g)(2)(iii), (g)(2)(viii), and (g)(2)(x) run afoul of the recent appellate decision in Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155 (4th Cir. 1998), contending that "a product is not a drug merely because a consumer uses it as one" and that "there must be proof as to the manufacturer's intent." The comment also cited National Nutritional Foods Ass'n v. Mathews, 557 F.2d 325 (2d Cir. 1977), to support its position that a manufacturer's intent, as determined from labeling or advertising, is the primary factor in determining whether a product is intended to treat a disease.

Although FDA disagrees with the Brown & Williamson decision and is awaiting the outcome of Supreme Court review, this rule does not depend on the resolution of the legal issues in that case. The focus of the rule is on express and implied claims made by the vendor in labeling. None of the provisions of the rule, including those mentioned in the comment, rely on consumer use as a standard for determining whether the product is intended to treat or prevent disease.

The rule is consistent with the decision in National Nutritional Foods Ass'n v. Mathews, in which the court said, "FDA is not bound by the manufacturer's subjective claims of intent but can find actual therapeutic intent on the basis of objective evidence. Such intent also may be derived or inferred from